cardiomyocytes *in situ* and *in vivo*), these potential uses are not part of the claims and do not serve as limitations. Rather, the claimed invention is directed to a method of introducing a nucleic acid into cardiomyocytes using a recombinant AAV vector which is infused into a coronary artery or a coronary sinus. Whether the cardiomyocytes and coronary artery or coronary sinus are *ex vivo* or *in vivo* is irrelevant (see, *e.g.*, claim 40).

REMARKS

Claims 24-46 are pending in the application. Claim 24 is "objected to" as being "vague" for the recitation of the phrase "perfused by said artery or said sinus." Claims 24-26 stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement.

The Examiner objected to claim 24 as being vague for reciting "perfused by said artery and said sinus," and suggested amending the claim to recite "perfused through said artery or said sinus." Applicants request herein that the amendment to the claim be entered and request, therefore, that the objection be withdrawn.

In the Office Action mailed August 29, 2001, the Examiner rejected claims 24-46 under 35 U.S.C. § 112, first paragraph, as failing to meet the enablement requirement, and on the grounds that the scope of the claims is not commensurate with the scope of the enabling disclosure. To the extent that this rejection has not been withdrawn, Applicants incorporate by reference and reiterate the arguments in Applicants' Response mailed January 2, 2002.

In the Office Action mailed March 7, 2002, the Examiner rejected claims 24-46 under 35 U.S.C. § 112, first paragraph, as failing to meet the enablement requirement, and on the grounds that the claimed subject matter is not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

(1) The Scope of the Claimed Invention

The first paragraph of section 3 of the Office Action mailed August 29, 2001 asserts that the specification is enabling only for the method described in the working example shown on pages 10-11 of the specification and, by implication, suggests that the remainder of the specification enables no additional scope of invention. The Office Action does not, however, offer any reasoned explanation why the methods demonstrated to be operable in the working example would not be enabled for the scope of the claims.

In particular, the August 29, 2001 Office Action acknowledges that the specification is enabling for "transducing explanted and perfused hearts of C57BL/6 mice", but does not offer any explanation why one of ordinary skill in the art would not be able to perform the method of the invention with human or other mammalian hearts *ex vivo* or *in vivo*. Similarly, the Office Action acknowledges that the specification is enabling for transduction with 1.5x10E9 IU/g of recombinant AAV vector, but does not offer any explanation why one of ordinary skill in the art would not be able to perform the method of the invention with other titers of vector, including the specifically claimed ranges of about 1x10E5 to 1x10E9 IU/g (claims 31 and 34), or about 1x10E6 to 1x10E8 IU/g (claims 32 and 35), or about 6x10E7 IU/g (claims 33, 36 and 39). Similarly, the Office Action acknowledges that the specification is enabling for transduction with the AAV/CMV-lacZ vector, but does not offer any explanation why one of ordinary skill in the art would not be able to perform the method of the invention with AAV vectors including any desired nucleic acids other than the lacZ insert (claim 24), including the specifically claimed

nucleic acids encoding an anti-sense RNA or a protein (claim 41); an ion channel gene, a contractile protein, a phospholamban, a β adrenergic receptor, a β adrenergic kinase, a growth factor, an angiogenic factor, a protein or nucleic acid capable of inducing angiogenesis, or a protein or nucleic acid capable of inhibiting angiogenesis (claim 42); FGF-1, FGF-2, FGF-5, VEGF, or HIF-1 (claim 43); or thymidine kinase, p2l, p27, p53, Rb or NF-κB (claim 44). Finally, the August 29, 2001 Office Action acknowledges that the specification is enabling for transduction by infusion "for 15 minutes via catheter in the left common carotid artery," but does not offer any explanation why one of ordinary skill in the art would not be able to perform the method of the invention with infusion into a coronary artery or coronary sinus (claim 24) for any other period, including the specifically claimed periods of at least about 2 to 30 minutes (claims 28 and 34), about 5 to 20 minutes (claims 29 and 37), or about 15 minutes (claims 30, 38 and 39).

The Office Action mailed March 7, 2002 does not provide the missing explanations but, rather, attacks the utility of the working example and makes conclusory statements regarding non-enablement. In particular, the Office Actions states:

> The working example provided in the specification, i.e. expression of beta-gal in cardiomyocyte in vivo, does not enable therapeutic use of rAAV vector expressing any desired molecule for gene therapy in vivo. The working embodiment of the specification fails to provide a use for gene therapy in vivo and does not meet the requirement of 35 U.S.C. 101 because the lacZ embodiment is not taught to be useful in therapy, and the specification does not assert any specific or substantial utility for this specific embodiment nor does the evidence of record suggest a well-established utility for this specific embodiment. Consequently this embodiment does not meet the requirement of 35 U.S.C. 101 and the how to use requirement of 35 U.S.C. [112] first paragraph.
>
> Applicants argue that the specification enables a method of transducing cardiomyocytes by infusing a recombinant adeno-associated virus (AAV) vector comprising a nucleic acid expressing a desired molecule into a coronary artery or

> a coronary sinus and the Official action does not provide explanation for the enablement rejection of the claimed invention. Applicants further argue that the Official action only rejects the unclaimed subject matter, i.e. gene therapy (response p. 9-12). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 8-29-01 (Paper No. 15) and the reasons set forth above.

Unfortunately, there are no reasons set forth in either the August 29, 2001 or the March 7, 2002 Office Actions why one of ordinary skill in the art could not practice the claimed invention.

In order to make an enablement rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 27 USPQ2d 15 10 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). As stated by the court in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971), "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 169 USPQ at 370. MPEP 2164.04]

The Office Action of August 29, 2001, does not meet this burden. Rather, that Office Action merely recites the scope of the claimed invention, points out that the claimed invention reads on unclaimed subject matter (*i.e.*, gene therapy), and then argues that the unclaimed subject matter is not enabled. Therefore, the rejection is improper.

Similarly, the Office Action of March 7, 2002, does not meet this burden. Rather, that Office Action merely insists that unclaimed limitations must be read into the claims, attacks the utility of the working example, and then attacks the enablement of the working example. As 35 U.S.C. §101 and 35 U.S.C. §112 require, respectively, utility and enablement for the claimed invention, rather than for unclaimed subject matter or working examples, the rejection is improper.

Therefore, for the foregoing reasons, Applicants respectfully submit that they are not entitled to a scope of protection equal to only the working examples in the disclosure, and that the pending claims are enabled in accordance with 35 U.S.C. § 112, first paragraph, by a disclosure which describes each element of the claimed invention and includes working examples demonstrating the operability of the claimed invention.

(2) The Claimed Invention is Enabled

An analysis of an enablement rejection requires a determination of whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent application coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). A patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444

(Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984). MPEP 2164.01.]

Submitted herewith under 37 C.F.R. 1.132 is a Declaration of Michael S. Parmacek, M.D. (the "Parmacek Declaration"), in support of the enablement of the claimed invention. The twenty-one references cited in the Parmacek Declaration but not previously of record are disclosed on the accompanying Form 1449. Copies of these references are enclosed with this Response.

As established by his declaration and *curriculum vitae* (¶¶ 1-4 and 21; Exhibit 1), Dr. Parmacek was one of ordinary skill in the art at the time the invention was made. The declaration also establishes that Dr. Parmacek has read the application and understands the claimed invention (¶¶ 6 and 8-9).

As established by the Parmacek Declaration, at the time of the invention, the construction of a recombinant AAV vector encoding a desired molecule operably linked to a control region would have been routine (¶ 11); many proteins and antisense RNA sequences useful for treating cardiovascular conditions were known, and cloned DNA encoding these proteins and RNA sequences was readily available (¶ 12); the specification contains sufficient guidance for the preparation of high titers of AAV vectors and determination of the amount of AAV vector needed to transduce cardiomyocytes in a given animal (¶ 13); intraventricular or intracardiac injection of rAAV encoding therapeutic molecules was known to have therapeutic effect (¶ 17); and it was well known that rAAVs were particularly suited for use as gene transfer vectors (¶ 20).

Dr. Parmacek concludes that the application, coupled with the knowledge in the art, "enabled one of skill in the art to practice the claimed invention in December 1998" (¶ 27). Specifically, Dr. Parmacek concludes that "[b]ased on such teaching and guidance in the Leiden application, along with the state of the art described herein with respect to molecular biological techniques and *in vivo* gene transfer, it was merely a matter of routine experimentation to construct a recombinant AAV vector encoding a desired molecule, deliver it to an animal by infusion into a coronary artery or coronary sinus, and thereby transduce cardiomyocytes" (¶ 27). Moreover, Dr. Parmacek points out that since the filing of the application, "others in the field have done nothing more than follow the teaching of the Leiden application and successfully transduce mouse cardiomyocytes using rAAV vectors encoding the marker gene β-galactosidase under the control of the CMV promoter (¶ 28).

Thus, for at least the foregoing reasons, Applicants submit that the rejections are improper and should be withdrawn.

(3) Utility of the Claimed Subject Matter

In order to meet the utility requirement of 35 U.S.C. 101, an applicant can establish that the claimed subject matter has a "well established" utility. That is, an applicant can establish that the claimed subject matter has a specific, credible, substantial utility which is well known, immediately apparent, or implied by the specification's disclosure, alone or taken with the knowledge of one skilled in the art.

The Parmacek declaration establishes that the utilities of the disclosed methods of transducing cardiomyocytes would be immediately apparent and recognized as well-established by one of ordinary skill in the art at the time the application was filed (¶ 22). Such utilities

include, for example, transducing non-human animal hearts *in vivo* to create animal models for human cardiovascular disease (¶ 22).

Applicants are required to provide only one utility for the claimed subject matter and have done so. Therefore, Applicants respectfully submit that the claimed invention has a credible, specific and substantial utility which is recognized to be well-established in the art by one of ordinary skill in the art, and which is sufficient to meet the utility requirement of 35 U.S.C. §101, and the "how to use" requirement of 35 U.S.C. §112, first paragraph.

(4) Enablement of Unclaimed Subject Matter

The Office Action of August 29, 2001 stated that "[a]lthough the new claims have been rewritten to 'a method of introducing a nucleic acid encoding a desired molecule into cardiomyocytes by infusing a recombinant AAV vector into a coronary artery or a coronary sinus' the claims still read on *in vivo* gene therapy." The Office Action then proceeds to argue against the enablement of gene therapy.

The Office Action of March 7, 2002 states:

> As discussed in the preceding Official action, the claims are directed to gene therapy *in vivo* in light of the specification. Gene therapy *in vivo* is the sole use for the claimed method in light of the specification.

The Parmacek declaration contradicts the assertion that the sole utility of the claimed invention is gene therapy (¶ 22). Thus, in short, the Examiner has decided to ignore the claimed subject matter and to base enablement rejections on unclaimed subject matter. This is not consistent with the law.

Claims may read on much subject matter that is unclaimed, and may still be enabled. Merely as an example, a claim to a screw may read on a perpetual motion machine which

comprises a screw (in combination with other parts). The claim to the screw may nonetheless be enabled even if the unclaimed perpetual motion machine cannot be. Similarly, a claim to a method of rocket propulsion may read on a method of space flight which includes the use of propulsion method (in combination with other steps). The claim to the method of rocket propulsion may nonetheless be enabled even if the unclaimed method of space flight is not.

The claims of a patent must be limited such that they define an invention which is novel and nonobvious over the prior art, and the claimed subject matter must have at least one credible, specific and substantial utility. The claims need not, however, be limited to specific utilities unless necessary to distinguish over the prior art.

Therefore, irrespective of whether the present invention may be used in methods of gene therapy, and irrespective of the Examiner's beliefs regarding the enablement of gene therapy, the claims to methods of transducing cardiomyocytes are enabled and have at least one utility immediately apparent and recognized by one of ordinary skill in the art. The enablement of the claimed methods and their utility is established by the Parmacek declaration submitted herewith.

Therefore, in light of the foregoing, Applicants respectfully submit that they are not required to enable every possible utility of the invention, including unclaimed limitations read into the claims from the specification, and that the pending claims are enabled in accordance with 35 U.S.C. § 112, first paragraph, by a disclosure which describes each element of the claimed invention and includes working examples demonstrating the operability of the claimed invention.

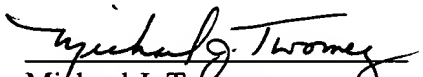
SUMMARY

Claims 24-46 are pending in the application. Claim 24 is amended herein. No new matter is added by the amendment.

Applicants request that the Examiner reconsider the application and claims in light of the foregoing Response, and respectfully submit that the claims are in condition for allowance. If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

A petition for a one-month Extension of Time for Response is submitted herewith. The Commissioner is hereby authorized to charge the fee for the petition, and any other fees now required to maintain the pendency of the application, to Deposit Account No. 08-0219.

Respectfully submitted,
Hale and Dorr, LLP



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MARKED-UP COPY OF AMENDED CLAIM

24. (Amended) A method of introducing a nucleic acid encoding a desired molecule into cardiomyocytes which comprises:

infusing a recombinant adeno-associated virus (AAV) vector into a coronary artery or a coronary sinus for a time and in an amount sufficient to stably and efficiently transduce cardiomyocytes perfused [by] through said artery or said sinus, wherein said AAV vector comprises at least one nucleic acid operably linked to a control region, said nucleic acid encoding said desired molecule.